

Remarks

Following entry of this amendment, claims 1, 4-8, 12-21, and 23-24 are pending. Claims 2-3 and 9-11 are canceled herein. Claims 1 and 8 are amended, as supported throughout the specification, such as (but not limited to) pages 1 and 13-14 and the original claims.

Applicants believe no new matter is added herein. Reconsideration of the subject application is respectfully requested.

Telephone Interview

Applicants thank Examiners Ford, Foley, Minnifield and Modesi for the helpful interview of July 23, 2008, with the undersigned and Dr. Finzi, wherein the outstanding rejections were discussed.

Rejections Under 35 U.S.C. § 103

Claims 1-15 and 23-24 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jahanshahi et al (Journal of Neurology, Neurosurgery and Psychiatry, 1992, 55:229-231) in view of Binder (U.S. Patent No. 5,714,468 published February 3, 2998) and further in view of Carruthers et al (U.S. Patent No. 6,358,917 B1 published March 19, 2002). The claims as amended are directed to the injection of a neurotoxin to the corrugator supercilii or the procerus muscle to cause paralysis of the corrugator supercilii or the procerus muscle in order to treat depression. Applicants respectfully disagree with this rejection as may be applied to the claims as amended.

Jahanshahi et al. teach that depression in torticollis patients is secondary to the postural abnormality of the head (see page 229, first column), and constitutes “a reaction to the disorder.” Botulinum toxin was injected into the superficial neck muscles (not facial muscles) of subjects to treat torticollis (see page 229, second column). The aim of the results presented by Jahanshahi et al. was to assess “improvement of torticollis with botulinum toxin injection accompanied by improvement of depression, reduction of disability, and improvement of the negative body concept and low self esteem” (see page 229, second column). Jahanshahi et al. report that the injection of botulinum toxin into the superficial neck muscles results in straightening of the head and relief from neck pain, and *reduction of depression and disability associated with head position and pain* (page 231, first column). Jahanshahi et al. conclude that the improvement of depression was a “non-specific result” and that it

“provides support for the reactive nature of depression and disability in a proportion of torticollis patients” (page 231, second column). Thus, Jahanshahi et al. only suggest the treatment of subject with a skeletal muscular disorder. Contrary to the assertions made in the Office action (see page 5) Jahanshahi et al. simply do not suggest, nor render obvious the selection of any subject without torticollis, let alone the selection and treatment of a subject with dysthymia or major depression.

Binder teaches the reduction of headache pain by injecting botulinum toxin. Binder et al. suggest the extra-muscular injection of botulinum toxin. Binder et al. do not suggest, nor render obvious, the selection and treatment of any subject with dysthymia or major depression.

Caruthers et al. teach the cosmetic use of botulinum toxin to paralyze the depressor anguli oris muscle to alleviate downturn of a subject's mouth. Caruthers et al. teach the cosmetic effect of botulinum toxin. Caruthers et al. do not suggest the use of a toxin to treat any emotional disorder, let alone a depression or dysthymia.

The claims include the step of selecting a subject with selecting a subject diagnosed with major depression or dysthymia using specific clinical criteria for major depression or dysthymia. As discussed previously, according to the DSM-IV, a person suffering from Major Depressive Disorder must have a depressed mood or a loss of pleasure in daily activities for at least two weeks. Major Depression is not due to substance abuse or bereavement, nor is it caused by a general medical condition, such as torticollis. Indeed, the DSM-IV discloses that the symptoms of major depression are NOT due to a physical illness, alcohol, medication, street drugs or normal bereavement (documentary evidence provided with the response to the Office action dated January 16, 2008).

The claimed methods are not obvious over the prior art of record. According to the MPEP § 2141, rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior

art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed methods. In the present application, this burden has simply not been met by the U.S. Patent and Trademark Office.

As argued previously, there is nothing in the teachings of Jahanshahi, on the treatment of torticollis (a spastic muscle condition of the neck) and injection of Botulinum toxin into the neck that would suggest to one of ordinary skill in the art, such as a physician, to combine these teachings with Caruthers et al. on a cosmetic use to alleviate downturn of the mouth. Furthermore, a physician would not look to a headache treatment (such as that taught in Binder) for alleviating cosmetic issues or for treating a severe condition such as torticollis. Thus, there is nothing in the prior art, absent the present specification, that would lead one of skill in the art to combine teachings on the treatment of torticollis with a treatment for a headache or with teachings of how to cosmetically improve the face. Medical treatments used for one of these conditions simply does not prompt variations based on medical treatments used for a completely different condition, with a completely different etiology.

Submitted herewith is the Declaration of Dr. Bruce Capehart under 37 C.F.R. § 1.132. Dr. Capehart is a staff psychiatrist for the Department of Veterans' Affairs, and one of skill in the art. Dr. Capehart confirms that Jahanshahi et al. does not suggest to a psychiatrist that Botulinum toxin should be used to treat depression in the absence of underlying torticollis. Dr. Capehart states that the innervation of the neck is through the spinal root of the accessory nerve (CN XI) and branches of the second and third cervical nerves (C2 and C3). The corrugator supercilii has innervation from a dual nerve supply with contributions from branches of the frontal, zygomatic and buccal branches of the facial nerve. The procerus has innervation through the buccal branch of the facial nerve. Thus, given a physician's understanding of anatomy and physiology, a psychiatrist, neurologist or any other physician reading Jahanshahi et al. would not predict that injections of Botulinum toxin into the neck to have the same effect as injection of Botulinum toxin into the corrugator supercilii or procerus muscle, *as the innervation is entirely different. Thus, there is a scientific basis to support the assertion that the claimed invention would not be obvious to one of ordinary skill in the art, based on any of the prior art of record.*

The Declaration of Dr. Capehart confirms that a psychiatrist would not look to a therapeutic modality for torticollis to treat major depression, nor would they look to headache medications (such as taught by Binder) to provide a route of administration for a psychiatric disorder such as major

depression (which has entirely different symptoms and etiology from either a headache or torticollis), nor would they combine these teachings with teachings on cosmetic applications, as taught by Carruthers et al.

Not only does Dr. Capehart's Declaration provide evidence that one of skill in the art would not be motivated to combine the cited prior art, it provides evidence that there is a missing element in the present rejection. Specifically there is nothing in Jahanshahi et al., Binder et al. or Carruthers et al. that suggests to a one of skill in the art to select a subject with depression using the accepted clinical characteristics for these diseases, such as would be delineated in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) or the Beck Depression Inventory, and or to treat a subject with major depression Botulinum toxin by injection into the corrugator supercilii or the procerus muscle.

The claims are amended herein to be limited to methods for treating depression that include the injection of a neurotoxin in to the corrugator supercilii or the procerus muscle Also submitted herewith is the Declaration of Dr. Finzi under 37 C.F.R. § 1.132. Dr. Finzi compared the effect of the injection of Botulinum into the different muscles of the face for treating depression. Results are presented in the specification for three patients. These patients were diagnosed with major depression or intermittent anxiety/depression. Botulinum toxin was administered to the corrugator supercilii or the procerus muscle of each of these subjects. The injections treated the depression of all of these subjects, who all reported improvements in their mood. However, Dr. Finzi's Declaration documents that injection of Botulinum toxin into other muscles of the face, such as the lateral orbicularis oculi and the frontalis muscle does not treat depression. The injection of Botulinum toxin into the the corrugator supercilii or the procerus muscle provides an unexpectedly superior result for the treatment of depression, as compared to injection of Botulinum toxin into the orbicularis oculi.

The orbicularis oculi and the frontalis muscle are also innervated by the facial nerve. Dr. Capehart's Declaration states that differences in the innervation of the muscles of the neck and the face provide evidence that one of skill in the art would not predict that Botulinum toxin would be of use to treat depression based on Jahanshahi et al. (alone or in combination with Binder and/or Carruthers et al.). However, the corrugator supercilii, the procerus muscle, the frontalis muscle and the orbicularis oculi all have common innervation, as they are innervated by the facial nerve. The fact that

administration of Botulinum toxin to the corrugator supercilii or the procerus muscle was effective for the treatment of depression, while administration to the orbicularis oculi or the frontalis muscles was not effective for the treatment of depression (even though all of these muscles are commonly innervated) supports the conclusion that claimed methods provide an unexpected superior result.

Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 16-21 were also rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jahanshahi et al., in view of Binder and Carruthers et al., further in view of Wagstaff et al.

Jahanshahi et al., Binder et al., and Carruthers et al. are discussed above, both individually and in combination.

Wagstaff et al. teach that paroxetine (a selective serotonin reuptake inhibitor, SSRI) is effective at treating depression, obsessive-compulsive disorder, and panic disorder. Wagstaff et al., teaches that SSRI inhibitors are of use to treat depression. Thus, Wagstaff et al. is silent on treatments for torticollis, headache, and cosmetic procedures (indeed SSRIs would be ineffective for the treatment of torticollis, wrinkles or headache). Thus, Wagstaff et al. does not make up for the deficiencies of Jahanshahi et al., Binder or Carruthers.

SSRIs are not used to treat the muscle spasms of torticollis or headaches, and are not used for cosmetic purposes. With regard to torticollis, Diller et al., (Fluoxetine-induced extrapyramidal symptoms in an adolescent: a case report, Swiss Med Wkly 2002;132:125-126, copy attached) teach that SSRI treatment can result in torticollis. Similarly, Kaplan & Sadock's Pocket Handbook of Clinical Psychiatry, Lippincott Williams & Wilkins, 2005, page 418 (see http://books.google.com/books?id=Fwcrfk2BjEsC&pg=PA418&lpg=PA418&dq=SSRI+torticollis&source=web&ots=cqf-4EUG8N&sig=qxCP618vNVQQAZG8PNc3utQFJIY&hl=en&sa=X&oi=book_result&resnum=4&ct=result#PPA418_M1, available on the internet) teaches that a side effect of selective serotonin reuptake inhibitors is that they can cause torticollis. Thus, torticollis is a contraindication for treatment with a SSRI. In view of the known side effects of SSRIs, one of skill in the art would not combine the teachings of Janhanshahi et al. (on the treatment of torticollis) with Wagstaff et al. (on selective serotonin reuptake inhibitors).

Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

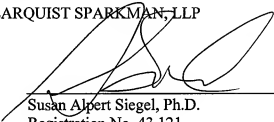
Applicants believe the present application is ready for allowance, which action is requested. If any matters remain to be discussed before a Notice of Allowance is issued, Examiner Ford is respectfully requested to contact the undersigned for a telephone interview at the telephone number listed below.

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